JOURNAL OF
Pediatric Ophthalmology & Strabismus®

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112 **Pseudo-Brown's Syndrome Secondary to a Growing Conjunctival Dermolipoma**
Hayyam Kinali, MD; Sinan Tatlipinar, MD; Ali Sefik Sanac, MD; and Sevgül Bilgic, MD

114 **Ocular Involvement in Siblings With Familial Mediterranean Fever**
Ahmet Akman, MD; Birgül Varan, MD; Yonca A. Akova, MD; and Pinar Aydin, MD, PhD

117 **Rufous Albinism**
J.S. Mehta, MBBS; P. Good, PhD; D. Mahanaj, MBBS; L. Butler, FRCOphth; S. Bundey, FRCP; and J. O'Shea, FRCOphth

Departments

59 *Editorial*
Rudolph S. Wagner, MD

61 *Letters to the Editor*

96 *CME Quiz*

98 *Eye to Eye*
Medial Rectus Muscle Laceration
Panelists: Miles J. Burke, MD; Monte Del Monte, MD; and Patrick DeRespinis, MD

120 *Abstracts*

122 *Information for Contributors*

124 *Classified Marketplace*

The *Journal of Pediatric Ophthalmology & Strabismus* (ISSN 0191-3913; Canadian BN-12978 0466 RT) is published bi-monthly by SLACK Incorporated, 6900 Grove Road, Thorofare, New Jersey 08086-9447. Printed in the USA.

Subscription rates: Individual—$119.00 for 1 year; $189.00 for 2 years; $249.00 for 3 years. Institutional—$129.00 for 1 year; $209.00 for 2 years; $289.00 for 3 years. Outside the US add $49.00 per year. Resident rate in the US: $59.00 (a letter of certification indicating residency of the subscriber is required). New subscriptions will start with the next published issue. Single back issues are $29.00. Payment must accompany order. Subscription requests should be addressed to the publisher (except Japan). In Japan, contact Woodbell Incorporated, 4-22-11, Kitakasai, Edogawaku, Tokyo 134, Japan.

Change of address: Notice should be sent to the publisher 6 weeks in advance of effective date. Include old and new addresses with zip codes. The publisher cannot accept responsibility for undelivered copies. POSTMASTER: Send Form 3547 to the *Journal of Pediatric Ophthalmology & Strabismus*, 6900 Grove Road, Thorofare, New Jersey 08086. Periodicals postage is paid at Thorofare, New Jersey 08086-9447 and additional mailing offices. The *Journal of Pediatric Ophthalmology & Strabismus* is listed in Index Medicus, Ocular Resources Review, Medline, Excerpta Medica, Current Contents/Clinical Medicine, Sci-Search, and Research Alert.

Effect of Botulinum Toxin A Chemodenervation in Sensory Strabismus

Sueng Han Han, MD; Helen Lew, MD; Chang Woog Jeong, MD; and Jong Bok Lee, MD

Abstract

Purpose: To study the effect of botulinum toxin type A chemodenervation in sensory strabismus.

Methods: Twelve patients with sensory strabismus were treated with an injection of botulinum toxin type A (Botox; Allergan, Irvine, Calif). Botulinum toxin type A was diluted with 0.9% sodium chloride without preservative at a dose that ranged from 1.25-5 U. A Teflon-coated needle electrode was inserted into the medial rectus muscle in cases of esotropia and into the lateral rectus muscle in cases of exotropia. Four patients were treated with ≥2 injections of botulinum toxin type A. Changes in the angle of strabismus and related complications were followed for >6 months postinjection.

Results: The mean deviation before injection was 33.8 prism diopters (Δ) and the mean corrective effect on the deviation was 72.8% after injection in patients with sensory strabismus. The final deviation in 9 patients was <10 Δ. Complications were hypertropia in 3 (25%) patients and conjunctival hemorrhage in 1 (8.3%) patient.

Conclusion: Botulinum toxin type A is likely to prevent muscle contracture and affect muscle and neuronal tissues. This study on the effects of sensory strabismus with botulinum toxin type A injection suggests it has the potential to replace surgery or be used as an adjuvant therapy.

Journal of Pediatric Ophthalmology and Strabismus 2001;38:68-71.

Introduction

After Scott[1] reported in 1973 that Oculinum was effective in treating extraocular paralysis in an animal model, strabismus treatment with botulinum toxin type A was first used clinically in 1978. Initially, botulinum toxin type A chemodenervation was confined to the treatment of acute paralytic strabismus; however, recently, it has been used to treat many types of strabismus. In addition, botulinum toxin type A has been found to be effective in correcting small-angle deviations of <10 prism diopters (Δ) to 15 Δ, conditions that might be considered too minute for surgical intervention, but are still bothersome to the patient.[2] Botulinum toxin type A also can be a useful alternative for patients in whom general or local anesthesia is contraindicated. Furthermore, it is known to be safe and without systemic complications when repeatedly injected at

From the Department of Ophthalmology, Institute of Vision Research, Yonsei University College of Medicine, Seoul, Korea.

Originally submitted January 26, 2000.

Accepted for publication June 28, 2000.

Reprint requests: Sueng Han Han, M.D., Dept of Ophthalmology, Yonsei University College of Medicine, Yongdong Severance Hospital, 146-92 Dogok-Dong, Kangnam-Ku, Seoul, Korea.

TABLE

PATIENTS WITH SENSORY STRABISMUS TREATED WITH BOTULINUM TOXIN TYPE A

Patient No./ Sex/Age (y)	Initial Deviation (Δ)	Muscle Injected	No. Injections (U)	Follow-Up (mos)	Final Deviation (Δ)
1/F/29	20, left exotropia	Left lateral rectus	1 (2.5)	7	10, left exotropia
2/F/32	35, right exotropia 14, right hypertropia	Right lateral rectus	1(2.5)	8	8, right exotropia 4, right hypertropia
3/M/30	25, left exotropia	Left lateral rectus	1 (2.5)	6	Straight
4/F/46	25, right exotropia 10, right hypertropia	Right lateral rectus	1 (2.5)	6	6, right exotropia 6, right hypertropia
5/F/23	30, left esotropia	Left medial rectus	1 (2.5)	6	6, left esotropia 6, left hypertropia
6/M/28	45, left exotropia	Left lateral rectus	1 (2.5)	8	30, left exotropia
7/M/29	50, right exotropia	Right lateral rectus	1 (2.5)	6	25, right exotropia
8/F/52	50, right esotropia	Right medial rectus	2 (5.0,2.5)	7	30, right esotropia
9/M/51	10, left exotropia 18, left hypotropia	Left lateral rectus	1 (1.25)	6	18, left hypotropia
10/F/21	50, left exotropia 15, left hypertropia	Left lateral rectus	3 (2.5,2.5,2.5)	6	8, left exotropia 15, left hypertropia
11/F/42	35, right esotropia	Right medial rectus	2 (1.25,1.25)	6	6, right esotropia
12/M/26	30, right exotropia	Right lateral rectus	4 (2.5,2.5,2.5,2.5)	8	4, right hypertropia

short intervals under topical anethesia.[5] However, clinical experience is not comprehensive and the follow-up data are not extensive. This article reports the effects of botulinum toxin type A chemodenervation, which is believed to be a reversible treatment in sensory strabismus.

MATERIALS AND METHODS

From January 1996 to December 1998, 12 patients (5 men and 7 women) with sensory strabismus were treated with botulinum toxin type A (Botox; Allergan, Irvine, Calif). Average patient age was 34.1 years (range: 21-52 years) (Table).

Three patients underwent strabismus surgery. All patients underwent complete ophthalmologic and orthoptic evaluation including duction testing, Hirschberg test, and modified Krimsky test. The conjunctival surface was anesthetized with four or five repeated instillations of 0.5% proparacaine at 1- or 2-minute intervals. A 27-gauge, 1.5", Teflon-coated, monopolar electrode needle and ground electrode were connected to an electromyographic amplifier. Each patient was directed to look away from the field of action of the injected muscle, and then, without conjunctival incision, the needle electrode was placed in the insertion site of the muscle. The patient was asked to slowly look toward the field of action of the injected muscle. The needle was inserted along the muscle 25-30 mm posteriorly until a loud crackling noise was heard and the fluid was then injected. Botulinum toxin type A was diluted with 0.9% sodium chloride without preservative in a dose ranging from 1.25-5 U. The needle was inserted into the medial rectus muscle in cases of esotropia and into the lateral rectus muscle in cases of exotropia. Four patients were treated with ≥2 injections of botulinum toxin type A. Changes in the angle of strabismus and complications of botulinum toxin type A were followed for >6 months after last injection. Data were analyzed with the Statistical Analysis System (SAS) program, and the statistical method used was the Wilcoxon rank sum test.

RESULTS

Mean deviation angle before injection was 33.8 Δ and 10.8 Δ at 6 months postinjection. The mean deviation correction achieved was 23 Δ (72.8%) and the final deviation in 9 patients was <10 Δ. In three cases, in which the patients underwent a subsequent surgery, the mean corrected deviation was 74.3%. In the remaining patients, the mean corrected deviation was 72.7%. However, there was no

statistically significant difference (P=.852) between these groups. In 3 patients, residual horizontal deviations >10 Δ were noted after 6 months of follow-up. These patients refused additional injections or surgery (Table).

Complications included hypertropia in 3 (25%) patients and conjunctival hemorrhage in 1 (8.3%) patient. Complications of hypertropia were noted in 3 patients. In 1 patient, the deviation disappeared after 6 months of follow-up (Table). In the remaining 2 patients (patients 5 and 12), the amount of residual hypertropias after 6 months of follow-up was within 10 Δ, and the patients showed no discomfort; therefore, surgical intervention was not undertaken. The commonly reported complication of ptosis did not occur and no systemic complications were observed.

Discussion

The seven antigenically distinct forms of botulinum neurotoxin (type A to G) are produced by the bacterium *Clostridium botulinum*. Botulinum toxin type A is easily made in deep culture and has a high molecular weight of 900,000 d.[3,4] Botulinum toxin type A interrupts the release of acetylcholine from the nerve terminal, although it does not interrupt the storage of acetylcholine in vesicles.[4] The toxin acts progressively on the motor nerve terminal and causes the end-plate potential to approach an irreducible quantity. Botulinum toxin does not interrupt the transmission of the nerve impulse and does not influence any electrical excitement or transmission in either the nerves or muscles.[3,4]

Botulinum toxin acts for a long period as it attaches firmly to the muscle and is rarely absorbed systemically. While other toxins were found in the blood 25 days after oral administration, type A toxin is fixed to the peripheral nerve system and tissue and is not found in the circulatory system. In the toxin-hemagglutinin complex, 900,000 d did not pass through the intestinal wall after oral administration. It is known that complexes of 150,000 d are found in the vascular system. The probability of the toxin passing the blood-brain barrier is low. It has been reported that if a large amount of toxin is injected, a small amount is transferred to the central nervous system through the vascular system. Because the onset of botulinum toxin is slow, its onset with doses of 1×10^{-3} pg and 1.6×10^{-3} μg is 2 or 3 days after injection, and its peak effect is achieved 5 or 6 days postinjection.[3,4]

The basic concept of the botulinum toxin type A effect, in the case of nonparalytic strabismus, is that the injected muscle is weakened and stretched by the antagonist, which is contractured secondarily. As the neuromuscular block by botulinum toxin type A disappears, deviation of the eyeball decreases. The injection site in esotropia is the medial rectus muscle and the injection site in vertical deviation is the vertical muscle, but not the oblique muscle.[5-7] In paralytic strabismus, botulinum toxin type A is usually injected as an antagonist of the paralytic muscle. The antagonist muscle is weakened and stretched and the deviation corrected. Secondary deviation due to antagonist contracture in paralytic strabismus is prevented or decreased.[8] It was reported that since the paretic antagonist is stretched further, ocular deviation is orthophoric when extraocular muscle paresis has partially or completely recovered, allowing surgery to be performed more easily.[5-7]

Recent studies have shown that botulinum toxin type A may have a permanent therapeutic effect, and two theories have been proposed. The first is that botulinum neurotoxin type A inhibits Ca^{2+}-dependent K^+-evoked release of acetylcholine, noradrenaline, and dopamine from rat cerebrocortical synaptosomes, where cholinergic terminals were most susceptible. Interestingly, none of the conditions could reverse the toxin-induced blockade of evoked release, which led to the conclusion that toxin-sensitive components exist in all nerve terminals that are concerned with transmitter release.[9] The second theory is that persistent muscular atrophic change was acquired in adult monkey extraocular muscles by injection of botulinum toxin type A into muscle. Spencer et al[10] reported the injected muscle fibers appeared normal and the vasculature recovered in proportion to the decreased cross-sectional area of the muscle fibers. On the basis of these findings, one of the long-term consequences of botulinum toxin paralysis of the extraocular muscle may be a change in the length-tension and fatigue characteristics of the extraocular muscles.[9,10]

In horizontal strabismus, botulinum toxin type A injections reduce the deviation by approximately 65%. Single injection can be expected to reduce the deviation to <10 Δ in approximately 30%-35% of patients.[2] Most patients, however, require more

than one injection, with the average number of injections varying anywhere from 1.3 to 2, depending on the type of strabismus and the size of the original deviation.[7,11,12] In vertical strabismus, botulinum toxin type A reduced the deviation by an average of 17 Δ, resulting in 41% reduction. These patients received an average of 1.7 injections and underwent follow-up for at least 6 months.

In consecutive strabismus, deviation was corrected in 87% of patients who were overcorrected and in 40%-60% of patients who were undercorrected. It has been reported that in childhood strabismus, the success rate is 65% in exotropia and 45% in esotropia.[3] In sensory strabismus, we found the mean deviation before injection was 33.8 Δ and the mean deviation 6 months after injection was 10.8 Δ. Therefore, the mean correction of deviation was 23 Δ (72.8%) and the deviation of 9 patients was <10 Δ.

Side effects and complications associated with botulinum toxin type A injection into an extraocular muscle are scleral perforation, retrobulbar hemorrhage, Adie's pupil, conjunctival hemorrhage, and headache. Postinjection complications are ptosis, vertical strabismus, and diplopia. Patients complained of diplopia due to temporary palsy, but the diplopia disappeared when the effect of the toxin decreased.[2,8,13,14] Complications in our study were hypertropia in 3 (25%) patients and conjunctival hemorrhage in 1 (8.3%) patient. However, ptosis did not occur, and no systemic complications were observed.

Conclusion

Botulinum toxin type A is used to prevent muscle contractures and produce permanent changes in muscle and nerve tissues. Botulinum toxin type A chemodenervation is a safe, easy, and inexpensive alternative to surgery for the treatment of strabismus. In addition, we expect the clinical indications for botulinum toxin type A chemodenervation will be extended. This study on the effects of sensory strabismus with botulinum toxin type A injection suggests it has the potential to replace surgery or be used as an adjuvant therapy.

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